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The present invention concerns capsules to the application of active ingredients, the rapid in body openings, z. B. in the oral cavity or after rectal or vaginal application disintegrate.

Most drugs become oral administered in either solid or liquid dosage form. Solid dosage forms (z. B. Tablets or capsules) are swallowed, arrive into the stomach and set the drug free, which is then absorbed in the gastro-intestinal tract or local works. For some patients, z. B. Children or older patients, is swallowing solid medicine forms however difficult and can to Compliance problems (z. B. Nichteinnahme or Ausspucken of the medicine form) lead. Also swallowing solid medicine forms without liquid is not possibly difficult or. With journeys the ingestion solid dosage forms with water from hygienic reasons frequent is not recommendable. Also with animals the application of solid a body systems is difficult.

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Therefore various solid dosage forms developed, which can dissolve rapid in the oral cavity (mouth saliva, became) and be swallowed then without liquid. DE 27 44 493 C2 describes a dosage form in tablet form with porous matrix, prepared by lyophilization, which dissolves in the mouth saliva within fewer seconds. In addition a wirkstoffhaltige autoklavierte gelatin solution in preformed recesses (z becomes. B. a blister pack) given, frozen and by lyophilization into porous matrix (tablet) a dried. DE 40 18 247 C2 describes rapid folienförmige dosage forms disintegrating. The USA 5.762.961 and WHERE tablets, which disintegrate due to its high porosity rapid, describe 93/13758. The porosity becomes thereby by the removal of volatile adjuvants after the Tablettierung achieved. The USA 5.464.632 and the USA 5.178.878 describe rapid tablets disintegrating, which contain coated active substance particles. The rapid disintegration becomes thereby by the auxiliary material selection (z. B. Shower salts such as Natiumbicarbonat and citric acid) achieved and the poor taste of the active ingredient by an envelope with polymers reduced. With all these systems the active ingredient is into rapid matrix disintegrating an incorporated.

Beside these advantages the described rapid dosage forms disintegrating in addition, some disadvantages exhibit, like z. B. a mechanical stability lacking and an high moisture-sensitiveness.

The tablets prepared by lyophilization are very frangible, them can z. B. from a blister pack to be squeezed out, but removed do not have to become. Also will the tablet-like dosage forms usually with very much low hardness prepared, in order to make possible or reduce by the damage of coated active substance particles a faster disintegration due to the increased porosity.

Furthermore most rapid dosage forms disintegrating are also very moisture-sensitive and require a particular package.

Due to process engineering and product specific requirements frequent high auxiliary material quantities must become used, these technologies are therefore for high dosed active ingredients fewer suitable.

The object of this invention was therefore the development of a rapid dosage form disintegrating, which avoids many above that mentioned problems.

The object becomes according to invention comprising thereby dissolved that a capsule becomes the application from active ingredients to the order provided, at least a macromolecule disintegrating soluble in aqueous liquids rapid and/or or a mixture from at least two of these fabrics, whereby the capsule disintegrates after application into body openings rapid.

Furthermore the object becomes according to invention by the fact dissolved that a capsule becomes the oral application from active ingredients to the order provided, whereby the capsule disintegrates in the mouth or in the oral cavity rapid.

Furthermore the object becomes according to invention by the fact dissolved that a capsule becomes the vaginal, rectal or nasal application from active ingredients to the order provided, whereby the capsule disintegrates after introduction into the body opening rapid.

Furthermore the object becomes according to invention by the fact dissolved that a capsule disintegrates to rapid after introduction into body openings, which resulted from surgical interventions or injuries.

The macromolecule selected from natural and/or synthetic polymers, as proteins and peptides, is according to invention for example gelatin, albumin, polysaccharides, for example agar agars, alginates, Carageen, chitosan, dextrin, dextran, pectin, starch and its derivatives, Gummen, cellulose derivatives, for example hydroxypropylmethylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, polyacrylates, i.e. polyacrylic acid, polyacrylamide, polyethylene glycol, Polyvinylalcohol (also part-hydrolyzed), polyvinylpyrrolidone, Polyoxyethylenoxypropylen and copolymers from the compounds mentioned.

Prefered according to invention is a capsule, whereby as other adjuvants or several decay accelerator, swelling agent (source materials) and/or solubilizers or their mixtures are contained. Prefered one participates that the decay accelerator is selected out for example shower salts, sugar, sucrose, Sorbitol, Mannitol, sucrose.

Prefered furthermore according to invention is that other adjuvants, i.e. flavors, sweeteners, dyes, preservatives, gelling agents, fillers, pigments, wetting agent (surfactants) and softener are contained.

The capsule according to invention is furthermore characterised in that the cap covering micropores exhibits.

Prefered one is it furthermore that the cap covering encloses cavities in the form of gas bubbles.

It is according to invention provided that the capsule according to invention in the cap covering covers an active ingredient.

It is according to invention that the wirkstoffhaltige filling material is solid, semisolid or liquid.

It is furthermore according to invention that the active ingredient in retardierter form is present.

It is furthermore according to invention that the active ingredient in taste-masked form is present.

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An other subject-matter of the present invention is a drug, a comprising capsule according to invention and a pharmaceutical preparation contained in it, comprising at least a pharmaceutical agent and if necessary other pharmaceutical compatible Hilfsund of additives.

The object according to invention became thus disintegrating achieved with a rapid cap-like dosage form. Z becomes. B. active ingredient/auxiliary material mixture into a rapid cap covering disintegrating filled. The capsule disintegrates to rapid or separates rapid in the oral cavity auf/an, the solid or liquid filling material is then swallowed. Rapid one disintegrating is meant a far-seizing term and that the cap covering loses its form after application in the oral cavity rapid and rapid with the filling material be swallowed can. By movement of the capsule (z. B. by tongue movement) the disintegration can become positive affected. The decay time amounts to few minutes, prefered however less than 30 seconds.

The capsule according to invention exhibits a number of advantages.

Due to the smaller auxiliary material quantities higher active substance quantities can become and therefore high dosed active ingredients in comparison the known above dosage forms of the state of the art used.

Many active ingredients have a poor taste or must retardiert released to become and become therefore with polymer films coated. When injecting the coated drug in tablets the coat can become damaged and thus its function lost. With the tablets prepared by lyophilization the dispersion of the coated active substance particles in the aqueous gelatin solution before the lyophilization would cause the resolution of the envelope or a premature release of the active ingredient.

These problems do not exist the coated active substance particles with the cap-like dosage form, become z. B. no high press pressures exposed.

Furthermore also the mechanical problems and the moisture-sensitiveness are reduced/eliminated.

Used the according to invention cap material can be everyone in aqueous liquids soluble or material disintegrating. Prefered used one thereby macromolecules which dissolve or disintegrate rapid in waters. In addition both natural and synthetic polymers count, like proteins/peptides (z. B. Gelatin, albumin), polysaccharides (z. B. Agar agar, alginates, Carageen, chitosan, dextrin, dextran, pectin, starch and its derivatives, Gummen natural origin) of cellulose derivatives (z. B. Hydroxypropylmethylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose), polyacrylates (z. B. Polyacrylic acid, polyacrylamide), polyethylene glycol, Polyvinylalcohol (also part-hydrolyzed), polyvinylpyrrolidone, Polyoxyethylenoxypropylen and also corresponding copolymers.

With polymers the molecular weight plays an important role, cap materials with low molecular weight in ruins or separates usually more rapid. Furthermore high-concentrated liquid systems with the low molecular prepared can Oligo /Polymeren to become. The molecular weight of the polymers knows z. B. by hydrolytic or enzymatic degradation reduced become. With some polymers (z. B. Gelatin) knows the molecular weight z. B. by heating (z. B. Autopianos) reduced become.

The cap materials can become also in combination used.

To the interference of the disintegration rapid solvent adjuvants disintegrating/rapid (z can. B. Decay means such as shower salt or sugar and sugar derivatives such as z. B. Sorbitol, Mannitol, mannitol, sorbitol, sucrose) into the cap covering incorporated become. The disintegration can become also by the porosity of the cap covering affected. Gas bubbles can into the cap covering to the increase of the porosity and thus to the acceleration of the disintegration during the cap covering production (z. B. Dispersion of gas into the liquid with the immersing procedure) incorporated become. Alternative ones can become volatiles into the cap covering during the preparation incorporated, result in the cap covering porous after their removal.

Furthermore other adjuvants can become into the cap covering incorporated. In addition z count. B. Flavors, sweeteners, dyes, preservative, gelling agent (to the supporting formation of the cap covering, z. B. with the immersing procedure), fillers, pigments, wetting agent (surfactants) and softener. The capsules can become also with a thin layer coated, the z. B. the moisture-sensitiveness lowers or salivation positive affected. The active ingredient (also in "treated form" z. B. Micro /Nanopartikel) cannot become also during the cap production direct into the rapid cap covering disintegrating incorporated, the capsule can then either with filling material filled or also filled become.

The filling material of the capsule (cap contents) contains the active ingredient and, if necessary, of various adjuvants. The filling material can be solid, semisolid or liquid.

The dosage forms according to invention become normally used for active ingredients, which are absorbed in the stomach intestine channel or local to work. An absorption or a local effect in the oral cavity is however also possible.

Beside the oral use the capsule can become also in other body openings applied. In addition counts in particular the vaginal, rectal, nasal application way and also by surgical interventions or injuries developed body openings.

The dosage forms according to invention can become the administration of a variety of active ingredients or active substance combinations used. Possible drugs are in the text book of the pharmacology and toxicology "medicament effects" from E. Mutschier, scientific publishing house company ltd. listed.

A particular aspect of the invention is that the active ingredient in retardierter form can be present. The active ingredient knows z. B. in
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pellets (matrix of the reservoir pellets), microparticle (z. B. Mikrosphärulen or microcapsules) or colloidal particle (z. B. Nanoparticles, liposomes) incorporated its. Different retardierende materials used can become, z. B. Polymers with pH-dependent solubility (z. B. gastric juice-resistant polymers) or in stomach intestine juice insoluble polymers (z. B. Cellulose derivatives, acrylate derivatives, polyesters) or biodegradable polymers (z. B. Poly (lactid CO glycolide) or lipids.

Many active ingredients have a poor taste or odor. To the bypass of this problem corresponding additions can be added to the filling material or the active ingredient can coated or at ion exchange resin bound be.

If necessary the dissolution of active substance can be improved by known galenische methods (z. B. Dissolves in a suitable solvent, imbedding in Trägermaterialen, reduction of the particle size by physical or chemical methods - also nano-particle, nano-crystals, encapsulation into colloidal carrier particles, like z. B.) And the active ingredient in this form the filling material add to liposomes, lipid or polymer nano-particles or incorporated become.

Except drugs the dosage form according to invention can also for confectioneries, foods (and. A. Vitamins, mineral materials) and cosmetics (z. B. the mouth hygiene) to the oral use or ingestion used become.

The filling material can be both solid, and semisolid or liquid. The active ingredient or like the described above processed active ingredient dissolved and/or dispersed can become and become then in liquid form into the capsule filled in a liquid. The solid filling material can be present in powder or granular form or also in form small tablets or pellet or rapid matrix systems disintegrating.

The filling material knows adjuvants obtained beside the active ingredient also. In addition z count. B. Flavoring agent, flavors, sweeteners, decay means, wetting agent, dyes, flow regulating agent, fillers, bonding agents. Also a shower set can become the faster disintegration of cap contents or the taste improvement and excitation of salivation used. Also known adjuvants can be added to the person skilled in the art, which improve the mouthfeel of the dosage form.

Subject-matter of the invention are also methods to the preparation of the dosage form according to invention. The cap coverings can become by known cap manufacture procedures, the analogue preparation of soft or hard caps prepared. In addition z counts. B. the immersing procedure, with which into a liquid, which contains the cap materials/adjuvants, holds the liquid immerses kapselförmige metal pins to the pin surface and becomes after drying process the cap coverings obtained. The cap materials and other adjuvants become dissolved in a solvent or solvent mixtures (prefered aqueous) and/or. dispersed. With melting cap covering materials the cap coverings can become also by immersion of the pins in the melt and subsequent cooling prepared. The size and form of the cap covering by the size and form of the pins one contributes.

In another method the capsules become prepared by means of injection mouldings, with which the Kapselmasse in preformed forms will enter.

The capsules can become by those the person skilled in the art prior art methods with the filling material filled and sealed.

Examples for the macromolecules, adjuvants, filling materials useful in this invention and methods can apart from the technical literature also in corresponding text books (z. B. Modern Pharmaceutics, Marcel Dekker; Pharmaceutical Dosage form: Tablets, band 1-3, Marcel Dekker; The Theory and Practice OF Industrial Pharmacy, Lea & Febiger; Pharmaceutical technology, Thieme publishing house; Pharmaceutical technology, Fischer publishing house; The capsule; APV PAPER-bake, scientific publishing house company ltd.) to be found.

The subsequent examples describe the invention:

Example 1

Kapselförmige of dipping pins (cap-large 00) became into an heated autoklavierte gelatin solution (20-40%), in which Glycerol and Sorbitol dissolved became, immersed and again withdrawn. After drying process the cap halves of withdrawn, cut were plugged together and. The cap coverings disintegrated in the oral cavity into less than 30 seconds.

Example 2

Kapselförmige of dipping pins (cap-large 00) became into a autoklavierte gelatin solution (20-40%), in which Glycerol and Sorbitol dissolved became and were this-by-craved to fine air bubbles, immersed and again withdrawn. After drying process the cap halves withdrawn, were plugged together cut, and. The cap coverings disintegrated in the oral cavity into less than 30 seconds.

Example 3

2 capsules prepared after example 1 or became filled with a mixture from lactose and microencapsulated Paracetamol (taste-masked, with ethyl cellulose coated) before plugging the cap coverings together. The capsules disintegrated in the oral cavity into less than 30 seconds.

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Example 4

2 capsules prepared after example 1 or became filled with a mixture from microcrystalline cellulose, shower salt and Propranolol HCl Retardpellets (with ethyl cellulose coated) before plugging the cap coverings together. The capsules disintegrated in the oral cavity into less than 30 seconds.

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1. Capsule to the application of active ingredients, comprising at least a macromolecule disintegrating or a mixture from at least two of these fabrics, rapid soluble, in aqueous liquids and/or, whereby the capsule disintegrates after application into body openings rapid.

2. Capsule according to claim 1 to the oral application of active ingredients, whereby the capsule disintegrates in the mouth or in the oral cavity rapid.

3. Capsule according to claim 1 to the vaginal, rectal or nasal application of active ingredients, whereby the capsule disintegrates after introduction into the body opening rapid.

4. Capsule according to claim 1, whereby the capsule disintegrates to rapid after introduction into body openings, which resulted from surgical interventions or injuries.

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5. Capsule in accordance with one of the preceding claims, characterised in that the macromolecule selected is from natural and/or synthetic polymers, proteins, peptides, i.e. gelatin, albumin, polysaccharides, i.e. agar agars, alginates, Carageen, chitosan, dextrin, dextran, pectin, starch and its derivatives, Gummen, cellulose derivatives, i.e. hydroxypropylmethylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, polyacrylates, i.e. polyacrylic acid, polyacrylamide, polyethylene glycol, Polyvinylalcohol (also part-hydrolyzed), polyvinylpyrrolidone, Polyoxyethylenoxypropylen and copolymers from the compounds mentioned.

6. Capsule in accordance with one of the preceding claims, characterised in that as other adjuvants or several decay accelerators, swelling agent (source materials) and/or solubilizers or their mixtures are contained.

7. Capsule according to claim 9, characterised in that of the decay accelerators selected is from shower salts, sugar, sugar derivatives, sucrose, Sorbitol, Mannitol.

8. Capsule in accordance with one of the preceding claims, characterised in that of other adjuvants, i.e. flavors, sweeteners, dyes, preservatives, gelling agents, fillers, pigments, wetting agent (surfactants) and softeners contained are.

9. Capsule in accordance with one of the preceding claims, characterised in that the cap covering micropores exhibits.

10. Capsule in accordance with one of the preceding claims, thereby characterized; that the cap covering encloses cavities in the form of gas bubbles.

11. Capsule in accordance with one of the preceding claims, characterised in that the cap covering an active ingredient covers.

12. Capsule in accordance with one of the preceding claims, characterised in that the wirkstoffhaltige filling material solid, semisolid or liquid is.

13. Capsule in accordance with one of the preceding claims, characterised in that the active ingredient in retardierter form is present.

14. Capsule in accordance with one of the preceding claims, characterised in that the active ingredient taste-masked form is present.

15. Drug, a comprising capsule in accordance with one of the preceding claims and a pharmaceutical preparation contained in it, comprising at least a pharmaceutical agent and if necessary an other compatible auxiliary and additives.

The Delphion Integrated View

Title: **DE19922537A1: Darreichungsform zur Applikation in Körperöffnungen**

Derwent Title: Drug administration capsule for insertion in body cavities, e.g. mouth, rectum or wounds, containing rapidly dissolving or disintegrating macromolecular component to ensure rapid disintegration on administration [Derwent Record]

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Abstract: Beschrieben ist eine Kapsel zur Applikation von Wirkstoffen, umfassend mindestens ein in wäßrigen Flüssgkeiten lösliches und/oder rasch zerfallendes Makromolekül oder eine Mischung aus mindestens zwei dieser Stoffe, wobei die Kapsel in Körperöffnungen rasch zerfällt.

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1. Kapsel zur Applikation von Wirkstoffen, umfassend mindestens ein in wäßrigen Flüssigkeiten lösliches und/oder rasch zerfallendes Makromolekül oder eine Mischung aus mindestens zwei dieser Stoffe, wobei die Kapsel nach Applikation in Körperöffnungen rasch zerfällt.

Description Expand description

±

Die vorliegende Erfindung betrifft Kapseln zur Applikation von Wirkstoffen, die rasch in Körperöffnungen, z. B. in der Mundhöhle oder nach rektaler oder vaginaler Applikation zerfallen.

± Die folgenden Beispiele erläutern die Erfindung:
± Beispiel 1
± Beispiel 2
± Beispiel 3
± Beispiel 4

Foreign References:

PDF	Publication	Date	IPC Code	Assignee	Title
				BEECHAM	

☑	GB1552416		A61K 9/48	GROUP LTD	PHARMACEUTICAL COMPOSITIONS
	US5955454		A61K 9/08	ADIR ET COMPAGNIE	Nasal pharmaceutical composition containing a progestogen
	US4402692		A61K 31/48	SHIONOGI + CO. LTD.	Medicament capsules for rectal application
	US3664341		A61F 15/00	SCHMID, JULIUS, INC.	VAGINAL CAPSULE
	EP0374359A2		A61K 9/00	PHARMACAPS INC	Chewable, edible soft gelatin capsule
	WO9624337A1		A61K 9/00	SIJBRANDS, Gerrit, Jan	ORAL DOSAGE-FORMS CONTAINING A 'beta'-LACTAM ANTIBIOTIC
	WO8404675A1		A61K 9/00	BOISEN, Henrik	VAGINAL CAPSULES
	WO8705804		A61K 9/20	BOLHUIS, Gerad, Klaas	METHYLPREDNISOLONE/SODIUM CARBOXYMETHYL STARCH TABLET COMPOSITION
☑	JP03255024A		A61K 9/48	TOKAI CAPSULE KK	SOFT CAPSULE READILY MELTABLE IN MOUTH

Other References:

- DAB 8. Ausgabe S. 273
- Datenbank WPS auf EPOQ, DPMA München benutzt am 8.5.00, AN 1998-454918: RU 2102981 C1

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